This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/814,357	03/21/2001	De-Chao Yu	348022001600	3927

24353 7590 12/10/2003

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	24

DATE MAILED: 12/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,357	YU ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,63,72-74 and 77-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,63,72-74 and 77-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/2/03 has been entered.

Claims 62, 63, 72-74, and 77-85 are pending examination.

Applicants' traversal in paper no. 22 filed on 7/2/03 and the cancellation of claims 1-61, 64-71, 75 and 76, the amendment to claims 62, 81, and 82 in paper no. filed on 9/2/03 is acknowledged and considered.

Specification

The disclosure is objected to because of the following informalities: page 117 recites, "Figure 613." There is no Figure 613.

Appropriate correction is required.

Claim Objections

Applicant is advised that should claims 72-74 be found allowable, claims 81-83 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an

application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Response to Arguments

Applicant's arguments, see paper no. 22, filed on 7/2/03, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 59, 60, 62, 63, 72-75, and 76-79 has been withdrawn because of the cancellation of claims 59, 60, 75 and 76 and the amendment to the independent claims. See page 5.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 72-74 and 77-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 72-74 and 77-83 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: how the body of the claim completes the pre-amble of the claim. The preamble of the claim recites, "administering to a mammal synergistic combination," however, the body of the claim does not recite a synergistic combination. Instead

the body of the claim recites an additive combination and not a synergistic combination. The definition of a synergistic combination is: interaction of discrete agencies, agents, or condition such that the total effect is greater than the sum of the individual effects. See Merriam-Webster's Collegiate Dictionary, Tenth Edition, Springfield, Massachusetts, USA, 2001, synergism, page 1192.

Claim Rejections - 35 USC § 103

The rejection of claims 81-83 under 103(a) has been withdrawn because of the amendment to the claims to depend from claim 80.

Claims 72-74 and 77-83 are rejected under 103(a) because the claims do not define a synergistic combination and read on an additive combination.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 62, 63, 72, 73, and 77-82, 84, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (US Patent No. 5,871,726) taken with Gurnani et al. (Cancer Chemother. Phamacol., Vol. 44, pp. 143-151, 1999).

Henderson teaches a method for suppressing tumor growth comprising introducing an adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element comprising an enhancer for prostate specific antigen and a promoter into a tumor cell, wherein the introduction of the vector results in suppression of tumor growth (column 44, claim 30). Furthermore, Henderson teaches that the adenovirus gene essential for propagation is the adenoviral early gene, E1A or E1A and E1B (columns 10- 11 and column 15). Henderson further teaches using intravenous or intra-tumoral injection of the adenovirus to treat a tumor in a mammal (column 25, lines 1-23). The adenovirus, which is transcriptionally competent in target cells, may be used to kill the cells. To further ensure cytotoxicity, one may have one or more transgenes present, which have cytotoxic

effect. In this way one can provide high confidence that the target cells will be destroyed while providing for the appropriate level of expression of the cytotoxic agents. However, Henderson does not teach specifically teach a method using a replication competent adenoviral vector comprising administering to a tumor a target cell-specific adenovirus vector, wherein said vector comprises an adenoviral gene essential for replication under control of a target cell-specific TRE and an anti-neoplastic agent selected from the group consisting of paclitaxel, docetaxel, doxorubicin, and etoposide, at a dose level effective for suppressing tumor growth when administered alone.

However, at the time the invention was made, Gurnani teaches that p53 adenovirus combined with doxorubicin, paclitaxel, methotrexate, or etoposide inhibited cell proliferation more effectively than chemotherapy alone (pages 145-150). Gurnani teaches using doxorubicin (4mg/kg) and etoposide at amounts that are contemplated by the specification for suppressing tumor growth at a dose less than the effective does for suppressing tumor growth when administered alone (see pages 49-50 of the specification for the concentration range of alkaloids used in chemotherapy).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to use the adenoviral vector taught by Henderson in the combination method for suppressing a tumor in a mammal taught by Gurnani. One of ordinary skill in the art would have been motivated to use the replication competent adenovirus vector taught by Henderson in the method taught by Gurnani because Henderson teaches that replication competent adenoviral vectors may be used for its cytotoxic effect and because the replication

competent adenoviral vector would be restricted to target cells compared to the replication defective adenoviral vector taught by Gurnani.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/2/03 have been fully considered but they are not persuasive.

In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. In view of the totality of the prior art, one of ordinary skill in the art would have been motivated to use the adenoviral vector taught by Henderson in the method taught by Gurnani because using the replication competent adenoviral vector in the method taught by Gurnani would result an improved method of inhibiting the growth of cancer cells compared to using the replication defective adenovirus taught by Gurnani. Furthermore, since the adenoviral taught by Henderson and the anti-neoplastic agents taught in the combination method for treating tumors by Gurnani have different mechanism of suppressing tumor growth as stated by applicants (see page 6 of applicants' traversal) and the specification does not teach that the combination would not provide a beneficial combination, one of ordinary skill in the art would have been expected that the combination would result in a beneficial combination. In addition, since the adenovirus and the anti-neoplastic agents have a different mechanism of action for suppressing tumor then one of

ordinary skill in the art would determine that the adenovirus would not interfere with the anti-neoplastic agent.

In response to applicants' argument that, "In the absence of applicants teaching, it could not have been predicted that a beneficial result would have been obtained". See pages 6-7. The argument is not found persuasive because MPEP § 716.01(c) states:

> The arguments of counsel cannot take the place of evidence in the record. In re Schulze,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

Claims 73, 74, 77, 80, 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson (US Patent No. 5,871,726) taken with Gurnani (Cancer Chemother. Phamacol., Vol. 44, pp. 143-151, 1999) in further view of Duque (Cancer Gene Therapy, Vol. 6, pp. 554-563, 1999).

The rejection of the base claims 73, 77, and 82 under 35 U.S.C. 103(a) is applied here as indicated above, by Henderson taken with Gurnani. However, Henderson taken with Gurnani does not teach specifically teach a combination method using a replication competent adenoviral vector comprising administering to a tumor a target cell-specific adenovirus vector, wherein said vector comprises an adenoviral gene essential for replication under control of a target cell-

specific TRE, wherein the gene essential for replication is the adenoviral early gene E1B with a deletion of the 19-kDa region and an alkaloid at a dose less than the effective does for suppressing tumor growth when administered alone.

However, at the time the invention was made, Duque teaches that 19-kDa and 55-kDa E1B-deficient adenovirus induced marked cytopathic effect on malignant cells that was higher than that seen for wild type adenovirus (abstract). In addition, such adenovirus exerts a tumor suppressor effect *in vivo*. Duque teaches the 19-kDa protein in adenovirus inhibits the apoptotic pathway induced by expression of the Ad E1a protein (page 555).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to modify the adenovirus taught by Henderson as taught by Duque and use the modified adenovirus in the combination method for suppressing tumor growth in a tumor in a mammal taught by Gurnani. One of ordinary skill in the art would have been motivated to modify the adenovirus by deleting the 19-kDa region and using the modified vector in combination with any alkaloid in a method of suppressing growth of a tumor cell in a mammal because Duque teaches that deleting the 19-kDa region can induce a higher cytopathic effect in malignant cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/2/03 have been fully considered but they are not persuasive for the reasons set forth above. Applicants have not added any new arguments other than the arguments set forth in the previous 103(a) rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE - Art Unit 1635, can be reached at (703) 306-3217.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER